IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kari Alitalo et al.

Application No.: 10/774,802 | Confirmation No.: 9059

Filed: February 9, 2004 | Art Unit: 1647

For: THERAPY TARGETING FLT4 (VEGFR-3) EXPRESSED IN BLOOD VESSELS | Examiner: Ian Dang

DECLARATION UNDER 37 CFR 1.132 OF SIRPA JALKANEN, M.D. P.HD.

I, Sirpa Jalkanen, M.D., Ph.D., do hereby declare as follows:

I. INTRODUCTION

A. My background and experience and relationship with the patent applicant.

1.1 I currently work as a Professor of Immunology at the University of Turku in Finland, and a Research Professor at the National Institute for Health and Welfare (THL, former National Public Health Institute, KTL) in Finland. Additionally, I am the Director of 'Host Defence Research', one of the Centres of Excellence of the Finnish Academy. I also am the head of the Receptor programme of the University of Turku and the MediCity laboratory. During my career in research, which extends over 25 years, I have studied the onset mechanisms of inflammatory diseases and cancer and new treatment possibilities for them. I have been acknowledged with numerous Finnish and international rewards for my research achievements. For example, I received in 2005 the renowned Anders Jahre prize from the University of Oslo, and, in 2008, I was awarded with the Matti Äyräpää prize by the Finnish Medical Society Duodecim in recognition for active and successful medical research. I have authored over 200 published scientific journal articles relating to the mechanisms of inflammatory diseases and cancer. Further, I am one of the founders of BioTie Therapies Oyj, the first Finnish listed biotechnology company. My curriculum vitae is attached hereto as Appendix A.

1.2. I am neither an inventor nor owner of the patent application identified above ("the patent application"). I am acquainted with inventor Kari Alitalo, as we are both medical researchers in Finland, and we have recently co-authored a scientific paper.

B. Purpose for providing this declaration.

1.3. I understand that the patent application is currently being examined by the U.S. Patent and Trademark Office, and has been rejected by the patent examiner. I am providing this declaration to provide my opinion as a scientist on issues that may be relevant to the rejections and further examination of the patent application.

1.4. I understand that in one rejection, the U.S. patent examiner alleged that certain acronyms used in the claims of the patent application were indefinite, and I will analyze those acronyms in this declaration. I understand that in a second rejection, the Examiner alleged that the claims in the patent application (Appendix B hereto) define an invention that is an obvious variation of the invention that was claimed in U.S. Patent No. 6,824,777 (Appendix C hereto). I understand that the text of the patent application and the '777 patent are essentially the same, and the issue focuses on the differences between the claims of these documents.

C. Historical standard for review

1.5. I understand that the patent application has an effective filing date (for purposes of patentability and interpretation of terms) of October 9, 1998. Thus, the remarks that follow are remarks about what a scientist of ordinary skills and experience in the field of the invention would have understood words and phrases in the claims to mean in October, 1998.

II. INTERPRETATION OF SCIENTIFIC TERMS USED IN PATENT CLAIMS.

2.1. This section of my declaration relates to the question of interpretation of certain scientific terms, which may be relevant to the patent examiner's decision to reject certain claims as indefinite.

A. Use of the acronym "PAL-E" in claims of the patent application.

2.2. I understand that the patent examiner alleged that three terms used in the claims – "PAL-E" and "VEGFR-1" and "VEGFR-2" – were acronyms, and that such acronyms rendered the claims indefinite, in the absence of additional text spelling out what the acronyms represent.

2.3. A person who was asked to interpret these acronyms would observe that the claims provide an explanation (or context) for the acronyms.

Specifically, the claims state that "PAL-E" and "VEGFR-1" and "VEGFR-2" are blood vascular endothelial cell marker antigens. (See the language of claim 46, for example.) The invention involves cancer therapy and molecular biology, and scientists in these disciplines were familiar with the acronyms "PAL-E" and "VEGFR-1" and "VEGFR-2" by 1998 and understood the meaning of the acronyms. This would have been especially true for scientists familiar with blood vascular endothelial cell biology.

2.4. In October, 1998, the term "PAL-E" was used and understood by scientists in the cancer therapy and molecular biology disciplines to refer to an endothelial cell-specific monoclonal antibody (PAL-E antibody), or to the antigen to which the PAL-E antibody binds (the PAL-E antigen). Appendix D to this declaration contains abstracts of multiple scientific journal articles that referred to the antibody or antigen by the name of "PAL-E." As shown by Abstract No. 25 in Appendix D, Schlingemann et al., *Lab Invest.* 52(1): 71-76 (1985), these molecules and the term "PAL-E" were reported many years before the October 1998 filing date of the patent application.

2.5. If the word "antigen" or "antibody" is not used in an abstract or publication, the context in which the term "PAL-E" is used makes clear which (of the PAL-E antigen or the PAL-E antibody) is being referenced. In the claims of the patent application, it is clear that the PAL-E antigen is being referenced; the claims say "blood vascular endothelial marker antigen."

2.6. The acronym "PAL-E" refers to "pathologische anatomie Leiden-endothelium" (Niemela et al., Blood, 106(10): 3405 (2005), Appendix E). However, the literature and scientists in the field more frequently simply used the acronym. (See Appendix D.)

2.7. In summary, based on the state of the literature and conventional usage of "PAL-E," scientists in October of 1998 would have understood what was meant by the term/acronym "PAL-E" and certainly would have understood claim terminology such as "blood vascular endothelial marker antigen ... PAL-E." This term would not have caused uncertainty then (and would not cause uncertainty now).

B. Use of the terms "VEGFR-1" and "VEGFR-2" in claims of the patent application.

2.8. My analysis and conclusions are essentially the same with respect to claim language referring to blood vascular endothelial marker antigens VEGFR-1 and VEGFR-2. In October 1998, the terms "VEGFR-1" and "VEGFR-2" were used and

understood by scientists in the cancer therapy and molecular biology disciplines to refer to "Vascular Endothelial Growth Factor Receptor-1" and "Vascular Endothelial Growth Factor Receptor-2," respectively.

2.9. The receptors VEGFR-1 and VEGFR-2 were of interest in the scientific community, and scientists were familiar with the acronyms and used them in their scientific communications. As shown in Appendix F of this declaration, multiple scientific journal articles published before October 1998 used and/or defined these terms.

2.10. Because scientists understood what was meant by the terms/acronyms "VEGFR-1" and "VEGFR-2" by October 1998, these acronyms would not have caused uncertainty then (and would not cause uncertainty now).

III. PREFACE TO ANALYSIS ABOUT DOUBLE PATENTING

3.1. I understand that claims 1, 17, 32, 38, 50-52, and 53 of the '777 patent were cited by the patent examiner as claims that "encompass" the claims of the patent application. In the next sections of this declaration, I provide analysis of these claims (and the other claims of the '777 patent), and how they differ from claims in the patent application.

3.2. I understand that the claims of the '777 patent were initially not printed correctly, and that the U.S. Patent and Trademark Office issued a certificate of correction to fix the printing errors. Of particular note is the fact that claim 7 as printed is not a claim of the '777 patent, and was deleted.

IV. DIFFERENCES BETWEEN ANTI-FLT4 ANTIBODY CLAIMS OF THE '777 PATENT AND BISPECIFIC ANTIBODY CLAIMS OF THE PATENT APPLICATION.

4.1. One notable difference between some of the claims of the patent application and all of the claims of the '777 patent is that some of the application claims specify use of a bispecific antibody inhibitor. Claims 46, 68, and 69 are representative in that they refer to a bispecific antibody that binds both to Flt4 and to a blood vascular endothelial marker antigen, such as PAL-E, VEGFR-1, and VEGFR-2 discussed above. Many other claims of the patent application specify use of a bispecific antibody inhibitor. See, for example, claims 62, 72, 73, 78, 82, 90, 92, 99, 104, and 107.

4.2. The Examiner relied on claim 1 and 5 of the '777 patent to reject claim 46 of the patent application, arguing that "claim 5 of the '777 patent recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) ..." I understand that similar reasoning was used to reject other claims in the patent application, although sometimes different claims of the '777 patent were cited. (For example, claims 32 and 35 of the '777 patent specify using an inhibitor that can be an anti-Flt4 antibody, and the Examiner argued that "anti-Flt4 antibody in claims 32/35 of the '777 patent was "defined as a bispecific antibody," referring again to column 9, lines 60-67 of the '777 patent.) My analysis below is equally relevant to all of the claims in the patent application that specify using bispecific antibodies and all of the rejections of them for double patenting.

4.3. I disagree with the suggestion that a scientist in the field would use the term "anti-Flt4 antibody" when referring to a bispecific antibody. The term "anti-Flt4 antibody" would be used by scientists to refer to antibodies that bind to Flt4. Scientists would use the term "bispecific" to refer to dual affinity antibodies.

4.4. I also disagree with the patent examiner's reading of the '777 patent. I do not see any inconsistency between how a scientist in 1998 would have used the terms "anti-Flt4 antibody" and "bispecific antibody" and how the same terms were used in the descriptive portion of the '777 patent. In the patent, they are identified as different classes of inhibitor compounds.

4.5. Column 8, lines 9-16, of the '777 patent provides a generic statement of the invention involving *inhibitor compounds*:

> The invention also is directed to a method of treating a mammalian organism suffering from a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to the mammalian organism a composition, the composition comprising a compound effective to inhibit the binding of an Flt4 ligand protein to Flt4 expressed in cells of the organism, thereby inhibiting Flt4 function.

4.6. Anti-Flt4 antibodies are then discussed at Column 9, lines 55-59, as one example of an inhibitor compound. There is no mention in this paragraph of bispecific antibodies:

> For therapeutic methods described herein, preferred compounds include polypeptides comprising an antigen-binding fragment of an anti-Flt4 antibody, and polypeptides comprising a soluble Flt4 extracellular domain fragment. Human and humanized anti-Flt4 antibodies are highly preferred.

4.7. The paragraph beginning at Column 9, lines 60-67, explains that *another* class of *inhibitor compound* for practice of the invention is the bi-specific antibody:

> An expected advantage of the therapeutic methods of the invention lies in the fact that Flt4 is normally not expressed at any significant level in the blood vasculature of healthy tissues. In a highly preferred embodiment, the therapeutic compound comprises a bispecific antibody, or fragment thereof, wherein the antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

4.8. Thus, the descriptive portion of the '777 patent uses the terms "anti-Flt4 antibody" and "bispecific antibody" separately, to refer to two different types of inhibitor compounds that can be used for therapies described in the patent; an anti-Flt4 antibody and a bispecific antibody are *different embodiments* for practicing the invention. A scientist would not use these term interchangeably, and they were not used interchangeably in the '777 patent. Certainly, neither term was offered in the '777 patent as a "definition" for the other term.

4.9. In view of the foregoing analysis, I find nothing in the claims of the '777 patent that would have suggested to a person in the field to make or use for therapy a bispecific antibody that was immunoreactive with both Flt4 and a blood vascular endothelial marker antigen, such as PAL-E, VEGFR-1, or VEGFR-2. As discussed below in greater detail, the claims of the '777 patent fail to suggest anything about targeting blood vessels for therapy.

V. THE CLAIMS IN THE PATENT APPLICATION EMBODY A SURPRISING DISCOVERY THAT THE FLT4 RECEPTOR IS EXPRESSED IN BLOOD VESSELS OF CANCERS AND CAN BE A TARGET FOR TUMOR THERAPY.

5.1. Another noteworthy difference between all of the claims of the '777 patent and all of the claims of the patent application relates to Flt4 and blood vessels. The claims in the '777 patent are silent about Flt4 and blood vessels, whereas most of the claims in the patent application pertain in some fashion to targeting Flt4 expression in blood vessels for therapy and/or diagnosis, screening, or monitoring.

A. State of the art relating to Flt4 expression in October 1998.

5.2. In October 1998, the state of the art surrounding Flt4 expression, reflected in the scientific literature of that time, was that Flt4 was a marker for lymphatic endothelial cells in mature organisms. Flt4 expression was thought to be largely restricted to these cells, and not expressed in blood endothelial cells. Much of that literature was published by inventor Alitalo's laboratory, where Flt4 was discovered and characterized.

5.3. Kaipainen et al., *Proc Natl Acad Sci USA* 92: 3566-3570 (1995) and Lymboussaki et al., *Am J Pathology* 153(2): 395-403 (1998) (see Appendix G) exemplify the state of the knowledge surrounding Flt4 expression from the time of the discovery of Flt4 through the time that the patent application was filed in October 1998.

5.4. Kaipainen et al. (1995) analyzed Flt4 expression during mouse embryogenesis and in adult human tissues. It was observed that, during mouse embryogenesis, Flt4 expression became restricted to the lymphatics as the embryo matured. Kaipainen et al. taught that that Flt4 is a marker for lymphatic vessels and some high endothelial venules in adult human tissues. Specifically, Kaipainen et al. reported that Flt4 was expressed in the adult human lymphatic endothelia of the lung, mesenterium, and appendix, but was not expressed in adult human veins, arteries, and capillaries. (See, for example, Kaipaninen et al. at page 3569, last paragraph, first and second sentences.)

5.5. Lymboussaki et al. was published in August 1998, just before the October filing date of the patent application. This article also teaches that Flt4 was a marker for lymphatic endothelial cells in adult tissues, and not blood endothelial cells. Lymboussaki et al., which refers to Flt4 as VEGFR-3, taught, for example,:

> ...a specific marker for lymphatic endothelial cells would be more practical in histopathological diagnostics. Here we have applied a specific antigenic marker for lymphatic endothelial cells in the human skin, the VEGFR-3, and show that it identifies a distinct vessel population both in fetal and adult skin, which has properties of lymphatic vessels.
>
> (Lymboussaki et al. at pages 399-400.)

5.6. The discussion section of Lymboussaki et al. also reiterated the fact that Flt4 (VEGFR-3) is a marker for lymphatic endothelial cells, by stating:

> ...a specific marker for lymphatic endothelial cells would be useful, [e.g.,] in the diagnosis of lymphangiomas. Here we present such a marker, the VEGFR-3...
>
> (Lymboussaki et al. at page 399, second column.)

5.7. Lymboussaki et al. furthermore taught that VEGFR-3 (Flt4) is not a marker for blood endothelial cells. Lymboussaki et al. taught, for example, that the endothelial cells lining the blood capillaries containing red blood cells of cutaneous capillary hemangiomas had very little or no VEGFR-3 expression, as demonstrated by immunohistochemistry using anti-VEGFR-3 antibodies.

5.8. Moreover, Lymboussaki et al. taught that the difference in expression of VEGFR-3 among lymphatic endothelial cells and blood endothelial cells is useful in distinguishing between skin lesions involving lymphatic endothelium and skin lesions involving blood vascular endothelium. The last sentence of the abstract states:

> These results establish the utility of anti-VEGFR-3 antibodies in the identification of lymphovascular channels in the skin and in the differential diagnosis of skin lesions involving lymphatic or blood vascular endothelium.

5.9. The articles are representative of the knowledge and thinking about the Flt4 tyrosine kinase at the time that the patent application was filed in October 1998. Flt4 expression was thought to be largely restricted to lymphatic endothelial cells, so much so that Flt4 was considered to be a marker for lymphatic tissue. For example Flt4 was thought to be useful for distinguishing lymphatic vessels (which expressed Flt4) from blood vessels (which were thought not to express it).

B. References to Flt4 expression in the claims of the '777 patent would have been understood to refer to lymphatic expression.

6.0. Because the state of the art surrounding Flt4 expression in October 1998 was that Flt4 was a marker for lymphatic endothelial cells and not blood endothelial

cells, one of ordinary skill in the art who read the claims of the '777 patent would have understood all references in those claims to "cells expressing Flt4," and related phrases, as references to lymphatic endothelial cells.

6.1. For example, the Examiner cited claims 1, 17, 32, 38, and 50-53 in the Examiner's double patenting rejection. Claim 1 refers to inhibiting Flt4 receptor tyrosine kinase function in a mammal. This would have been understood to refer to Flt4 in the lymphatic system, because that was where scientists understood Flt4 was expressed.

6.2. Claim 17 of the '777 patent has a step of screening a mammalian subject to identify a neoplastic disorder characterized by cells expressing Flt4. Again, based on the state of knowledge of Flt4 in October 1998, that screening would have been understood to be a screening of lymphatics. Kaipainen et al. (1995) had reported, for example, that increased expression of Flt4 occurred in lymphatic sinuses and in metastatic lymph nodes and lymphangiomas, and these are the types of neoplastic expressions of Flt4 that would have been understood from the literature. There is no suggestion in claim 17 or any other claim of the '777 patent to screen for Flt4 in blood vessels.

6.3. A similar analysis applies to claims 32 and 53 of the '777 patent, which refers to treating a mammal with breast cancer characterized by endothelial cells that express Flt4. Based on the literature at the time that the application was filed, such as Kaipainen et al. (1995), this claim language would have been understood to be Flt4 expression in lymphatics, such as metastatic lymph nodes in breast cancer.

6.4. Likewise, claim 38 of the '777 patent refers to treating a mammal with a disease characterized by expression of Flt4 in cells. The literature had identified, e.g., metastatic lymph nodes in cancer and lymphangiomas (Kaipainen et al. (1995)) and lymphangiomatosis (Lymboussaki et al. (1998)). It would have been surprising and unexpected that Flt4 was expressed in blood vessel endothelia in certain diseases, presenting a new target for therapy.

6.5. Claims 50-52 of the '777 patent refer specifically to inhibiting genesis of lymphatic vessels in a mammal having a disease characterized by Flt4 expression. These claims explicitly refer to lymphatic vessels and lymph nodes, and suggest nothing about Flt4 in blood vessels.

C. A method directed to inhibiting genesis of blood vessels by targeting Flt4 would have been surprising and unexpected.

7.1. Claim 81 of the patent application is directed to a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase in blood vessels. (See the first three lines of claim 81.) The method uses any of a specified group of Flt4 inhibitors. As explained above, none of the claims of the '777 patent suggest that it would be possible to inhibit the genesis of blood vessels with these Flt4 inhibitors. Given that the state of the scientific literature that Flt4 was a marker for lymphatic endothelial cells and not blood endothelial cells, the method of claim 81 would have been surprising and unexpected from the claims of the '777 patent and the state of the art in October 1998.

7.2. At least claims 82 and 94 specify a similar purpose in the introductory portion of the claim, and are surprising and unexpected for the same reasons outlined for claim 81.

7.3. Claim 103 begins with a more specific statement of purpose – treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4. This statement of purpose is still focused on treatment targeted at blood vessel endothelial cells that express Flt4, which would have been surprising and unexpected from the claims of the '777 patent and the existing scientific literature in October 1998.

D. To screen patients for blood vessels expressing Flt4 to help with disease identification and choice of therapy would have been surprising and unexpected.

8.1. Each of claims 64, 67, 68, 87, 89, 90, 91, 92, 102, 106, 107, 110, 113, 116, and 121 of the patent application include a step involving screening a subject (mammalian or human) to identify a disorder (such as a neoplastic disorder or breast cancer) characterized by (i) **blood vessels which express Flt4** or (ii) **blood vessels which comprise endothelial cells expressing Flt4**.

8.2. For example, claim 64 recites:

> screening a human to identify breast cancer characterized by blood vessel endothelial cells expressing Flt4

and claim 67 recites:

> screening a human subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4...

Also, for example, claims 89 and 90 recite:

> screening a human subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4

and claims 91 and 92 recite:

> screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4...

Claims 102 and 107 recite:

> screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4

and claim 110 recites:

> screening for a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4...

Claims 68, 106, 116, and 121 each have similar language.

8.3. The screening language in amended claim 87 specifies "identifying a mammalian organism that is a human having a tumor characterized by blood vessels that express Flt4." The screening language in new claim 113 specifies "screening a human subject to identify tumor blood vasculature that expresses Flt4."

8.4. The screening steps of the claims of the patent application are different from the screening steps of the claims of the '777 patent, because the screening steps of the claims of the patent application consistently relate to screening for Flt4 in blood vessels or blood vessel endothelial cells. The claims of the '777 patent fail to teach or suggest anything about Flt4 expression in blood vessels, and certainly do not teach or suggest screening for blood vessel expression of Flt4 or a disorder characterized by blood vessels expressing Flt4 or blood vessels comprising endothelial cells expressing Flt4. (See discussion above, such as paragraph 6.2.) The idea embodied in each of these claims

in the patent application -- to screen patients for blood vessels expressing Flt4 to help with disease identification and choice of therapy – was not suggested and would be considered novel and surprising compared to the claims of the '777 patent.

E. To monitor therapy by monitoring Flt4 within blood vessels would have been surprising and unexpected.

9.1. New claim 114 for the patent application has not yet been considered by the examiner for double patenting analysis. It includes a step of monitoring the progression of a therapy with any of a group of inhibitors, where the monitoring involves measuring the quantity or distribution of Flt4 within blood vasculature. For all of the reasons discussed above, such a step would not have been suggested or expected from the claims of the '777 patent. Nothing in the claims of the '777 patent suggest to look for Flt4 expression in blood vessels for any purpose, be it screening (as discussed above) or monitoring (as specified in claim 114).

VI. CERTIFICATION

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

June 23, 2009
Date

Signature: Sirpa Jalkanen
Name: Sirpa Jalkanen, M.D., Ph.D.